

The University of Chicago

STUDIES ON THE POSSIBLE FUNCTIONAL
INTERRELATION BETWEEN THE THYRO-PARA-
THYROID APPARATUS AND EPINEPHRINE
SECRETION FROM THE ADRENAL
MEDULLA

A DISSERTATION SUBMITTED TO THE
FACULTY OF THE DIVISION OF THE
BIOLOGICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY

1939

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RUTH ELEANOR CORTELL

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AND EPINEPHRINE SECRETION FROM
THE ADRENAL MEDULLA

INTRODUCTION

Since the discovery of the parathyroid glands by Sandström (1) in 1880 and their rediscovery by Gley(2) in 1891, a large body of evidence has been built up which makes clear the complete functional independence of the thyroid and parathyroid glands. Recently an interdependence has again been postulated, from metabolic studies, but the evidence is not conclusive. In studying the possible existence of a functional interrelation between the thyro-parathyroid apparatus and epinephrine secretion, it is necessary to consider the thyroid and the parathyroid glands separately.

a. Thyroid

The possible functional interrelation among certain glands of internal secretion was emphasized by Eppinger, Falta, and Rudinger(3) in 1908. On the basis of metabolic studies, as, for example, the failure of injected adrenalin to cause glycosuria in thyroidectomized dogs, they postulated that the thyroid and the adrenal medulla (chromaffin system) have a mutual stimulating effect upon each other. Removal of one would depress the function of the other, and excess of either one would activate the other. Without any actual experimental data, they suggested, "Vielleicht wirkt das Schilddrüsensekret fördernd auf die Adrenalinproduktion ein und führt so bei Hyperthyroidismus zu einem erhöhten Erregungszustand des Sympathikus. . . ."

Since many of the symptoms of hyperthyroidism indicate a heightened activity of the sympathetic nervous system, and because adrenalin, when injected, acts upon those structures innervated by the sympathetic nervous system, many investigators have attempted to relate hyperthyroidism to increased epinephrine in the systemic circulation. Kraus and Friedenthal(4) in 1908, us-

ing the reaction of the frog's pupil to adrenalin, Fraenkel(5) in 1909, using the rabbit's uterus as a test object, and Brücking and Trendelenberg(6) in 1911, using the frog perfusion method, claimed to have demonstrated an increase in epinephrine in the peripheral blood serum of patients with exophthalmic goiter. O'Connor(7) in 1911 found that the frog perfusion method and the rabbit uterus method were not specific for epinephrine, but were actually detecting an epinephrine-like substance, which was supposedly liberated when blood clots and caused an increase in smooth-muscle tonus. He failed to detect any epinephrine at all in normal peripheral blood, using plasma instead of serum. Gottlieb(8) in 1911, likewise using plasma, found no epinephrine in peripheral blood in exophthalmic goiter patients. Stewart(9)(10) in 1912 showed that the tonus-stimulating substance, acting on the rabbit's uterus (and intestine) is present even in unclotted blood. Using a comparison of the results obtained with the rabbit's uterus and intestine, which react oppositely to epinephrine, but the same way to the tonus-increasing substance in blood, he could demonstrate no epinephrine in peripheral venous blood of normal people, nor in one patient with Graves' disease. In 1937, Maddock, Pederson, and Collier(11) reported the presence of epinephrine in peripheral blood of patients with hyperthyroidism and in postoperative thyroid crisis. They used the Whitehorn chemical method and biologic assay on the rabbit's uterus and intestine segments.

Experimentally there have been some studies on the effect of various thyroid extracts on the output of epinephrine from the adrenal glands. Ott and Scott(12) in 1912 injected crude gland extracts into urethanized cats, including thyroid and parathyroid extracts, and collected blood from the vena cava via a femoral vein catheter. The collected blood caused inhibition of the rabbit's intestine, but no quantitative studies were made. Gley and Quinquaud(13) in 1914 cannulated the lumbo-adrenal vein in dogs, so that only blood from the adrenals was collected. Control samples were compared with samples collected after the injection of extracts of desiccated thyroid as to their blood pressure-raising effect on a test dog. Only with large doses of thyroid was any increase in effect seen over the control blood, and the increase was comparable to that seen following the injection of extracts of other organs. Zunz and La Barre(14) in 1932 injected large

doses of thyroxin (0.5-3mgms/Kg.) into a donor dog whose pancreatic vein was anastomosed to the jugular vein of an adrenalectomized receiver dog. In 20-45 minutes, the blood sugar of the receiver dog fell to low limits, indicating to them that the thyroxin had stimulated the adrenals to put out epinephrine, which raised the blood sugar of the donor dog, causing an increased amount of insulin to be poured into the receiver dog. They also found that samples of adrenal vein blood gave maximum inhibition of the rabbit's intestine segment following the injection of thyroxin, but they made no quantitative measurements.

None of the experimental work contains any quantitative data on changes in epinephrine secretion due to an influence of the thyroid. In the study reported here, dogs were rendered hyperthyroid by feeding desiccated thyroid over periods of weeks, and their epinephrine output was determined, when they were in this state, by the method of Stewart and Rogoff, which allows quantitative estimations to be made.

b. Parathyroids

Although there seems to be some evidence for a functional interrelation between the parathyroid glands and the adrenal cortex(Rogoff,15), the evidence is not at all clear in the case of the adrenal medulla and the parathyroid glands. Eppinger, Falta, and Rudinger(16) in 1909 found that, whereas injected adrenalin did not cause glycosuria in thyroidectomized dogs, if the parathyroids were also removed, a profound glycosuria ensued. Falta and Rudinger(17) in 1909 claimed that injected adrenalin brought on symptoms of acute tetany in cases of latent tetany. They suggested that the parathyroids have an inhibitory effect upon the chromaffin system, and that in parathyroid insufficiency the supposed increased irritability of the sympathetic nervous system is aggravated by the excessive amounts of epinephrine in circulation. Guleke(18) in 1911, believing that the continuous outpouring of epinephrine is necessary for the maintenance of sympathetic tone, removed adrenals of dogs and cats in tetany, and claimed that tetany gave way to lassitude. But his experiments have little significance, as none of his animals lived longer than 60 hours, and many of them died within 12 hours. Georgopolous(19) in 1912 also postulating an antagonism between the parathyroids and the adrenal medulla, searched for increased epinephrine in

parathyroidectomized rabbits, but found none in peripheral blood, using the reaction of the frog's pupil. Nor were there any significant differences in epinephrine content of adrenals between control or experimental animals.

Some investigators of the effect of thyroid activity upon the adrenals, removed the parathyroids also, and inadvertently obtained the effects of acute parathyroid insufficiency. Gley(20) in 1914, determined the epinephrine content of the adrenals of dogs showing symptoms of parathyroid insufficiency, and found it to be the same as in normal dogs. Herring(21) in 1916 claimed that when thyro-parathyroidectomized cats showed symptoms of tetany, the epinephrine content of the adrenals was lower than normal. Czarnecki and Sarabia(22), in 1927, collected blood from the adrenal veins during splanchnic stimulation in dogs thyroidectomized 2-5 days previously, many of which showed symptoms of acute parathyroid insufficiency, and found that the blood pressure rise obtained upon reinjection into the same dog was the same as that from the adrenal vein blood of normal dogs collected under similar circumstances.

Many workers have reported that injected adrenalin causes a fall in serum calcium (Billigheimer(23), 1922; Lamelas(24), 1930). Bomskov(25) in 1932 reported that when calcium gluconate and parathyroid extract are injected simultaneously in rabbits, there is an immediate fall in blood calcium, previous to the usual rise. He postulated that the parathyroid hormone stimulates the output of epinephrine, to cause the fall, since, when he injected adrenalin without parathyroid extract, the calcium also fell. He determined the concentration of epinephrine in adrenal vein blood shortly after the injection of parathyroid extract, using the rabbit ear perfusion method of Pisemski, and claims to have demonstrated an increased concentration.

Binet and Weller(26) in 1933 reported a decreased epinephrine content of the adrenals of parathyroidectomized dogs, which did not appear if their blood Ca was maintained at a normal level. At most, this would indicate that normal blood calcium is required for upbuilding or storing of epinephrine in the glands. Bacq and Mathieu(27) in 1935 reported that dogs in chronic parathyroid insufficiency showed no change in epinephrine content of the adrenals, nor could Mathieu and Bacq(28) in 1934 find any effect of adrenalin in physiological doses upon the blood calcium

of such dogs.

As is the case in the thyroid studies, there are no reports of quantitative changes in epinephrine output due to disturbances in parathyroid function. In the work reported here, such a study was undertaken. Experimental hyperparathyroidism was produced by injecting parathyroid extract, and experimental hypoparathyroidism by removal of the parathyroids. Quantitative determinations of the rate of epinephrine liberation were made by the method of Stewart and Rogoff.

PROCEDURE

Dogs were used throughout this investigation. They were kept on a constant diet of boiled beef lung, white bread, and bone meal, with additions as the experimental procedures demanded.

Six dogs were used in the thyroid series. In all of the experiments, water intake and urine output were measured daily; pulse rate and body weight were determined at frequent intervals. In four dogs, rectal temperature was recorded at intervals. Although Kunde(29) in 1927 has shown that desiccated thyroid, fed in the doses which were used here, will certainly render dogs hyperthyroid, it was considered advisable to make observations of the basal metabolic rate in three dogs, one of which served as a control, to obtain an idea of the degree of experimental hyperthyroidism attained.

Basal metabolic rate was determined essentially according to the method described by Kunde(29). The dogs, trained to lie quietly, were fasted for 18-20 hours, and were rested for 30-40 minutes before beginning the observation. A specially devised mask was fitted to the animal and was connected with a Benedict-Roth closed circuit apparatus for the determination of oxygen consumption. Pulse rate and rectal temperature were taken at the conclusion of each observation; tests were made approximately four times each week throughout the course of the experiment.

A base line for each factor was determined, and then desiccated thyroid (Armour's, 0.2% iodine content) was administered orally, thoroughly mixed with the food. In only a very few instances did the dogs fail to eat this mixture. Doses ranged from 0.5 gms. to 1.3 gms. per kilogram of body weight daily, and the periods of administration ranged from 3 to 12.5 weeks.

At the conclusion of the period of thyroid feeding, the dogs were anesthetized with ether and a cava pocket made for the collection of adrenal vein blood, according to the method of Stewart and Rogoff. The samples were assayed for epinephrine concentration on the isolated rabbit's intestine. From the concentration of epinephrine in the adrenal vein blood and the rate of blood flow through the adrenals, the rate of output of epinephrine was calculated.

In the parathyroid series, ten dogs were injected subcutaneously with parathyroid extract¹ in doses varying from those which led to toxic symptoms, which would have undoubtedly resulted in death if continued, to doses which were smaller and repeated over longer periods of time. The dogs were sacrificed at various periods following the beginning of the extract injections, in order to determine their epinephrine output, by the method described above.

A second group of nine dogs were subjected to bilateral thyro-parathyroidectomy under Nembutal anesthesia, and when the typical symptoms of parathyroid insufficiency appeared, the rate of epinephrine output was determined. In five of the parathyroid-ectomized dogs, it was necessary to give supportive treatment when the symptoms suggested that the animal might die before the experiment could be concluded. Either parathyroid extract, calcium gluconate intravenously, or calcium lactate orally, was administered. The animals were usually allowed to show definite symptoms of parathyroid insufficiency again before being sacrificed for the determination of the epinephrine output.

In the operation for the removal of the parathyroid glands, the thyroid glands were also removed, making easier the removal of both internal and external parathyroids. Many workers have shown that extirpation of the main thyroid glands in adult dogs is without effect on this animal, presumably because of the existence of numerous accessory thyroid bodies. Therefore simultaneous removal of the thyroid does not seriously complicate the picture of parathyroid insufficiency.

In the parathyroid series, the state of parathyroid activity was followed by determining the serum calcium both before and

¹The parathyroid extract was generously supplied by Eli Lilly and Company.

during the experimental procedure. The Clark and Collip(30) modification of the Kramer-Tisdall method was used.

A series of eleven normal dogs served as controls for all the experiments. Their epinephrine output was determined in the manner described above.

The weights of the adrenal glands were recorded for each animal in the entire series of experiments. In the series of dogs which received injections of parathyroid extract, the weights of the thyroid glands were also recorded.

RESULTS

a. Thyroid

In the six thyroid-fed dogs, three of which were males and three females, definite symptoms of experimental hyperthyroidism were produced (see Table 1). All the dogs showed a fall in body weight; dogs 19 and 25, who were fed thyroid for longer periods of time showing the greatest percentage weight loss. The values for pulse rate, rectal temperature, and basal metabolic rate are tabulated as averages of the values recorded during the control period and of those during the experimental period. The latter usually showed a gradual increase during the period of thyroid feeding, so that at the conclusion of the experiment they were higher than the averages indicate. Each dog exhibited an increase in average pulse rate, and three of the dogs (19, 25, and 10) showed an increase in average rectal temperature over the control period. Dog 12 showed no average change in rectal temperature, but actually its temperature had risen to 102.7° when the experiment was concluded. Both thyroid-fed animals, one male and one female, whose metabolic rates were determined, showed an average increase of 61% and 49% respectively over the control averages. Urine output and water intake were increased in four of the dogs.

The adrenal epinephrine output in the experimental animals ranged within relatively narrow limits, with an average of 0.00013 mgm. per kilogram of body weight per minute for the entire series.

b. Parathyroid

i. Experimental hyperparathyroidism.--The results for this

TABLE 1
EPINEPHRINE OUTPUT IN EXPERIMENTAL
HYPERTHYROIDISM IN DOGS

Num- ber	Sex	Body Weight		Thyroid Fed		Average Pulse Rate		Average Rectal Temperature		Average BMR		Poly- uria	Epi- nephrine Output mgm./kgm. /min.
		Initial Kgm.	Final Kgm.	Daily Ave. Dose gm./kgm.	Duration Fed Weeks	Before Thyroid Fed /min.	After Thyroid Fed /min.	Before Thyroid Fed °F	After Thyroid Fed °F	Before Thyroid Fed Cal./kgm. /hr.	After Thyroid Fed Cal./kgm. /hr.		
19	M	11.2	8.6	0.9	12.5	53	80	100.5	101.3	1.54	2.48	0	0.00013
25	F	7.3	5.7	1.1	12.5	71	83	100.3	101.4	1.71	2.54	++	0.00010
3	M	13.3	11.0	0.5	6.0	54	76					0	0.00016
6	F	5.1	4.5	1.0	3.0	66	96					+++	0.00014
10	F	10.7	9.8	1.3	6.5	84	88	101.8	102.2			+++	0.00013
12	M	9.9	8.6	1.1	5.5	70	76	101.6	101.7			+	0.00013

series are shown in Table 2.

Dogs 41 and 44 each received a dose of 150 U of parathyroid extract (Lilly) in the morning and afternoon of the same day, and were sacrificed for assay of epinephrine output the following morning. Both showed a distinct rise in serum calcium, but no other symptoms.

Dogs 43 and 47 received an average dose of 190 U and 115 U respectively for three consecutive days, and their epinephrine output was determined on the fourth day. Dog 43 exhibited anorexia and dog 47 considerable vomiting. Autopsy on dog 47 revealed severe gastro-intestinal congestion and hemorrhage. The serum calcium determined on the fourth day was high in both cases.

Dog 60 received two injections of 50 U each within 4 hours, on the first day, and three injections at 4 hour intervals, on the second day. Epinephrine assay was performed on the third day. The serum calcium determined on the third day, was very high, and the dog exhibited marked anorexia and depression.

Dog 48 received an average daily dose of 38 U for five days; dog 55 received 50 U daily for thirteen days; and dog 56 received 50 U daily for twelve days. Epinephrine output was determined on the day following the last injection of parathyroid extract. Each of these dogs exhibited mild anorexia. The serum calcium rose in every case.

Dog 50 received 80 U daily and dog 57 received 50 U daily for five and six days respectively. Mild anorexia developed. Epinephrine output was determined two days after the final dose, when the blood calcium had returned to normal limits. A hemorrhagic gastric ulcer was found at autopsy in dog 57.

With the exception of dog 43, whose epinephrine output was 0.00004 mgm. per kilogram of body weight per minute, all of the parathyroid-injected dogs had epinephrine outputs which lay within the range for normal animals. The average epinephrine output for the ten animals is 0.000199 mgm. per kilogram per minute. The low output in dog 43 cannot be explained. Since this is the only animal with a definitely low output, it is impossible to attach significance to the result, at present.

The weights of the adrenal and thyroid glands showed no significant deviation from values for normal animals.

ii. Experimental parathyroid insufficiency.--The results for this series are shown in Table 3.

Dogs 38 and 74 were sacrificed for the determination of their epinephrine output at a time when they were exhibiting symptoms of extreme parathyroprivic tetany.

TABLE 2
EPINEPHRINE OUTPUT IN EXPERIMENTAL HYPERPARATHYROIDISM IN DOGS

Num- ber	Sex	Body Weight		Serum Calcium		Thyroid Weight		Adrenal Weight		Epinephrine Output mgm./Kgm./min.
		Initial Kgm.	Final Kgm.	Initial mgm./ 100 cc.	Final mgm./ 100 cc.	a gm.	b gm.	Right gm.	Left gm.	
41	M	8.6	8.4	9.56	14.74			0.41	0.43	0.00027
43	M	6.8	6.0	9.84	15.83			0.44	0.39	0.00004
44	M	8.6	7.7	11.44	15.37			0.73	0.63	0.00010
47	F	5.9	5.5	11.03	16.66	0.53	0.68	0.40	0.40	0.00012
48	F	5.4	4.3	11.05	16.63	0.19	0.25	0.38	0.38	0.00034
50	M	10.8	10.6	10.43	10.54	0.50	0.58	0.70	0.78	0.00022
55	M	9.1	7.7	9.88	15.29	0.87	0.87	0.43	0.49	0.00024
56	M	11.0	9.9	10.69	18.38	0.57	0.57	0.63	0.54	0.00011
57	M	10.7	9.7	9.31	11.71	0.48	0.65	0.82	0.65	0.00027
60	M	7.8	7.3	10.25	19.03	0.45	0.45	0.70	0.70	0.00028

TABLE 3
EPINEPHRINE OUTPUT IN EXPERIMENTAL PARATHYROID
INSUFFICIENCY IN DOGS

Num- ber	Sex	Body Weight		Serum Calcium		Appearance of Symptoms days	Adrenal Weight		Epinephrine Output mgm./Kgm./min.
		Initial Kgm.	Final Kgm.	Initial mgm./ 100 cc.	Final mgm./ 100 cc.		Right gm.	Left gm.	
21	M	11.7	10.1			8.0	0.73	0.76	0.000016
38	M	12.0	12.0	10.17	6.10	3.0	0.52	0.57	0.00017
61	M	8.8	8.5	11.85	7.44	1.5	0.40	0.40	0.00013
62	M	7.3	6.3	12.91	4.39	1.5	0.41	0.38	0.0009
68	F	9.8	8.8	10.02	4.03	4.0	0.64	0.64	0.000045
69	M	10.5	10.7	10.60	5.55	4.0	0.62	0.59	0.00021
71	M	7.3	7.5	11.66	5.28	2.0	0.49	0.50	0.00018
73	M	13.0	11.9	12.27	4.88	5.0	0.70	0.70	0.00020
74	F	8.0	7.6	10.88	5.76	2.0	0.56	0.56	0.00003

Dogs 68 and 73 were showing mild tetany, with some muscular fibrillations, when they were sacrificed for the determination of epinephrine output.

Dog 21 received 10 grams of calcium lactate daily for 2.5 weeks following the first appearance of symptoms of parathyroid insufficiency. Then the calcium lactate was discontinued and symptoms again developed. Epinephrine output was determined four days after discontinuance of therapy, the animal having clonic contractions.

Dogs 61 and 62 received 50 U and 30 U of parathyroid extract (Lilly) respectively when they first developed tetany. Epinephrine output was determined the following day. Blood calcium was low in each case.

Dog 71 received 100 U of parathyroid extract when tetany appeared. Symptoms were relieved. Four days later, muscular fibrillations were again evident, and the animal was sacrificed for the determination of its epinephrine output.

Dog 69 received 10 cc. of 10% calcium gluconate intravenously when tetany appeared. Three days later, muscular fibrillations were again evident, and the animal was sacrificed for the determination of its epinephrine output from the adrenals.

Final blood calcium in every case was well below normal. The adrenal weights were within normal limits. Dogs 21, 68, and 74 had epinephrine outputs of 0.000016, 0.000045, and 0.00003 mgm. per kilogram of body weight per minute, respectively. These values are definitely lower than normal. Dog 62 had a relatively high epinephrine output, while the remaining dogs in this series had outputs which were within the ordinary range.

c. Control Dogs

The results for this series are shown in Table 4. The epinephrine output in milligrams per kilogram of body weight per minute ranged from 0.00007 to 0.00037, with an average of 0.000181 for the series of eleven control dogs which were studied under the same conditions as the experimental animals. These figures compare quite well with those of Stewart and Rogoff(31) in their large series of observations.

DISCUSSION

The six animals which were fed desiccated thyroid were in a state of experimental hyperthyroidism as evidenced by the criteria relied upon. In every case, the epinephrine output was

TABLE 4
EPINEPHRINE OUTPUT IN CONTROL DOGS

Number	Sex	Body Weight Kgm.	Adrenal Weight		Epinephrine Output mgm./Kgm./min.
			right gm.	left gm.	
7.....	M	7.9	0.49	0.49	0.00007
8.....	M	8.1			0.00012
9.....	M	5.0			0.00011
14.....	M	11.5	0.62	0.75	0.00025
16.....	F	9.7	0.95	1.02	0.00009
17.....	M	12.9	0.55	0.53	0.00026
40.....	M	8.6	0.51	0.51	0.00023
54.....	F	6.5	0.51	0.51	0.00037
81.....	M	8.9	0.60	0.51	0.00008
82.....	M	8.3	0.45	0.56	0.00024
83.....	M	8.2	0.39	0.40	0.00017

within the limits found in normal animals. It is difficult to make comparisons of these results with those obtained by other investigators of this question (Ott and Scott(12), Gley and Quinquaud(13), Zunz and La Barre(14)) for a number of reasons. These workers evidently assumed that thyroid extract or thyroxin should act immediately. Kunde(29) demonstrated clearly, using the dog as the experimental animal, that injected thyroxin or ingested thyroid requires 7-12 hours to cause an effect, as determined by changes in the basal metabolic rate, which is probably the most reliable indicator of thyroid activity, at least in dogs. Furthermore, none of them made quantitative studies of the actual amount of epinephrine secreted by the animals in any of the experiments. Rough comparisons of the concentration of epinephrine in adrenal vein blood in control and experimental periods cannot yield information concerning the output, unless the rate of blood flow from the adrenals is known. Determination of the output of epinephrine depends upon the measurement of the concentration in relation to the blood flow from the glands. Stewart and Rogoff (32) showed that in normal animals, a change in blood flow results in a corresponding change in epinephrine concentration in the opposite direction, the output remaining constant.

The question of the presence of epinephrine in the sys-

têmic circulation in Graves' disease is one that is yet to be satisfactorily answered. The earlier workers used test objects which are not sensitive enough to detect such quantities as might be present in the systemic circulation. The conclusions of Maddock, Pederson, and Collier(11) are not entirely justified, since chemical methods for the detection of epinephrine in blood are non-specific and not sufficiently sensitive. Furthermore, their biological assays were not sufficiently controlled. The results reported here do not answer that question. Graves' disease is a disease of unknown etiology, in which the excessive thyroid secretion is usually a later development. In experimental hyperthyroidism, the excessive thyroid activity is produced early. It would seem from the results obtained in this study that the excessive thyroid activity, at least in dogs, has no demonstrable effect on epinephrine output, but what effect, if any, other factors which play a role in clinical hyperthyroidism may have on the adrenal medulla, cannot be determined until those factors themselves are clearly understood.

Excess of parathyroid hormone, in the form of the administered extract, produced no detectable effect on the rate of output of epinephrine from the adrenal medulla, in the animals investigated. In parathyroid insufficiency, three of the animals showed a lower epinephrine output than normal, which may represent a tendency toward a lower level in these animals. In view of the normal epinephrine output in other dogs of this comparatively small series of animals, it is difficult to draw conclusions until more data are available. It might be suggested that disturbances, in either direction, related to parathyroid activity may be capable of modifying the epinephrine output from the adrenals, also in either direction. This is suggested by the fact that one low output was found in the small series on hyperparathyroidism and three in the series on hypoparathyroidism. Also that, in the latter series, one relatively high output was observed. It is clear from these results, however, that extreme parathyroprivic tetany is not incompatible with the existence of a normal rate of output of epinephrine from the adrenal medulla. The same is true in hyperparathyroidism.

Earlier work on parathyroid-adrenal interrelations offers very little conclusive evidence either for or against such an interrelation. Georgopolous(19), Czarnecki and Sarabia(22), and

Bomskov(25) used methods of determining the epinephrine output which could not have yielded quantitative data. Not only were blood flow changes not taken into account, but epinephrine concentrations were determined on non-specific or insensitive test objects, such as the rabbit's ear perfusion or frog's eye method.

Determinations of the epinephrine content of the adrenals during various parathyroid disorders (Gley(20); Herring(21); Binet and Weller(26); Bacq and Mathieu(27)) do not reveal the functional state of the gland. It is well known that the content of epinephrine in the adrenal gland represents only a balance between the formation and liberation of epinephrine, and cannot by itself indicate the rate of secretion into the circulation.

It might be suggested that the use of an anesthetic in determining the epinephrine output would diminish effects that might have been present before the anesthesia was applied. For example, if experimental hyperthyroidism increases sympathetic irritability, and if the latter is reduced under anesthesia, its effect, if any, on the epinephrine output might also be reduced, thus leading to negative results. Similarly, in parathyroid tetany, the convulsions are abolished by anesthesia. It may be, then, that any effects that the actual convulsions would have on the epinephrine output might be reduced. However, many of the effects of the increased hormone, in the case of hyperthyroidism, and the decreased hormone, in the case of hypoparathyroidism are still present when anesthesia is applied. Any effects which these more chronic factors would exert on the output of epinephrine from the adrenals, either directly or indirectly, could not escape detection by using the method described above.

SUMMARY

Experimental hyperthyroidism induced by feeding desiccated thyroid had no detectable effect on the rate of output of epinephrine from the adrenals in dogs.

Experimental hyperparathyroidism induced by the administration of parathyroid extract had no detectable effect on the rate of output of epinephrine from the adrenals in dogs.

Surgical removal of the parathyroids, together with the thyroids, leading to occurrence of symptoms of parathyroid insufficiency, had no detectable effect on the rate of output of epi-

nephrene from the adrenals in five dogs, but appeared to lead to a reduced output in three dogs. These results require further experimental confirmation before final conclusions may be drawn.

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